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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,011	06/20/2003	Ciaran N. Cronin	SYR-AIK-5001-C1	5098

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 09/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/601,011	CRONIN ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6,9,12-15 and 17-30* is/are pending in the application.

4a) Of the above claim(s) *18-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6,9,12-15,17 and 26-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/3/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Appendix A*.

DETAILED ACTION

Status of the Application

[1] Claims 1, 4-6, 9, 12-15, and 17-30 are pending in the application.

[2] Applicant's amendment to the claims, filed on 7/5/2006, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's amendment to the specification, filed on 7/5/2006, is acknowledged.

[4] Applicant's amendment to the drawing figures, filed on 7/5/2006, is acknowledged.

[5] Receipt of an information disclosure statement, filed on 4/3/2006, is acknowledged.

[6] Applicant's arguments filed on 7/5/2006 in response to the Office action mailed on 4/4/2006 have been fully considered and are deemed to be persuasive to overcome the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[7] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Information Disclosure Statement

[8] With the exception of reference AB, all references cited in the information disclosure statement, filed on 4/3/2006, have been considered by the examiner. Reference AB has been lined through as it is a duplicate of reference A cited on Form PTO-892 attached to the Office action mailed on 4/4/2006.

Sequence Compliance

[9] This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See particularly the disclosed Figure 3 of the specification containing a list of atomic coordinates representing the disclosure of an amino acid sequence. When a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings. See MPEP § 2422.02.

Claim Rejections - 35 USC § 101

[10] Claim 30 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim drawn to a composition comprising a protein consisting of residues 125-391 of SEQ ID NO:1. The term "composition" in claim 30 can be interpreted to be a polypeptide and thus claim 30 can be interpreted as meaning a polypeptide comprising a protein consisting of residues 125-391 of SEQ ID NO:1. The claim reads on a product of nature and should be amended to indicate the hand of the inventor, e.g., by insertion of "purified" or "isolated." See MPEP § 2105.

Claim Rejections - 35 USC § 112, First Paragraph

[11] The written description rejection of claim(s) 1, 4-6, 9, and 12-15 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action. Claims 17 and 26-30 are included in the instant rejection for reasons that follow. Thus, claims 1, 4-6, 9, 12-15, 17, and 26-30 are rejected.

RESPONSE TO ARGUMENT: Applicant argues the claims as amended are all drawn to compositions and methods using residues 125-391 of SEQ ID NO:1, which has been crystallized by applicant, or SEQ ID NO:3, both of which are shown in Figure 1. According to applicant, the rejection is overcome by this amendment.

Applicant's argument is not found persuasive. The examiner maintains the position that the specification fails to describe all crystallized proteins as encompassed

by the claims. While the amendment to the claims limits the polypeptide of the composition, the recitation of "crystalline form" in claim 1 fails to distinguish the claimed genus of proteins in crystalline form from others, it does not specifically define any of the crystalline forms that fall within its definition, and it does not define any structural features commonly possessed by members of the genus of proteins in crystalline form that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus of proteins in crystalline form. In this case, the structure of the genus of proteins in crystalline form is completely undefined.

Applicant appears to take the position that by virtue of limiting the polypeptide of the crystalline form to residues 125-391 of SEQ ID NO:1, the genus of proteins in crystalline form is adequately described, however, it is well-known in the art that a single polypeptide can have a plurality of distinct crystal forms, which one cannot predict *a priori* (see, *e.g.,* Aleshin et al. *FEBS Lett* 434:42-46, 1998). Thus, as noted in the prior Office action, the genus of proteins in crystalline form encompasses species that are widely variant, encompassing species of crystal species of unliganded and liganded forms of residues 125-391 of SEQ ID NO:1, wherein the liganded form is in complex with *any* ligand. In this case, the specification discloses only a single representative species of the genus of recited protein crystals, *i.e.,* a crystal of residues 125-391 of SEQ ID NO:1 in complex with ATPγS having the space group symmetry $P6_122$ and having vector lengths a=b=80.45 Å, and c=172.18 Å (p. 24, Table 6), which diffracts X-rays to a resolution of 1.9 Å (specification at pp. 24-25, Table 6), and only a single

method for its crystallization, *i.e.,* the method disclosed at p. 48, ¶¶ [00198] and [0199] of the specification. Other than these single species, the specification fails to describe any other crystals of a protein consisting of residues 125-391 of SEQ ID NO:1 or methods for crystallization thereof as encompassed by the claims. MPEP § 2163 states "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." As such, the single disclosed species of crystals of a protein consisting of residues 125-391 of SEQ ID NO:1 and the single disclosed species of methods for making said crystal fail to describe all crystals and methods as encompassed by the claims.

It is noted that claims 4-6 limit the resolution, space group symmetry, or the unit cell dimensions of the crystalline form of claim 1. However, even these claims encompass widely variant species, considering that, while a crystal may diffract X-rays to a resolution of a resolution of 1.9 Å, the space group and unit cell dimensions are completely undefined, or while a crystal may have space group $P6_122$, the unit cell dimensions are completely undefined, or while a crystal may have unit cell dimensions of vector lengths a=80.45 Å, b=80.45 Å, and c=172.18 Å, the space group, which defines the symmetry of the crystal, is completely undefined. As such, the combination of these characteristics is required for adequate description of a protein crystal.

Claims 17 and 30 have been included in the instant rejection. According to MPEP § 2111, "[d]uring patent examination, the pending claims must be 'given their broadest reasonable interpretation consistent with the specification.'" Although not expressly

stated or defined in the specification, the "composition" of claims 17 and 30 has been interpreted as encompassing a composition comprising a protein in crystalline form, particularly as the instant application is directed to protein crystals. In this case, the specification fails to disclose even a single representative species of a crystal of SEQ ID NO:3. Even assuming *arguendo* the specification disclosed such a representative species, the specification would still fail to adequately describe all protein crystals of SEQ ID NO:3 for reasons noted above addressing claim 1. While applicant may argue that because of the similarity in sequence between residues 125-391 of SEQ ID NO:1 and SEQ ID NO:3 a crystal of SEQ ID NO:3 would have the same space group and unit cell dimensions, there is no way to predict *a priori* the space group and unit cell dimensions of a protein, as evidenced by the references of Kierzek et al. (cited in the prior Office action; see cited relevant teachings) and Buts et al. (*Acta Crystallogr. D.*, vol. 61, pages 1149-1159, 2005), which teaches that even a single amino acid mutation can alter the space group symmetry and unit cell dimensions of a crystallized protein. The specification fails to describe the composition of claim 30 for reasons noted above addressing claim 1.

It is also noted that claims 15 and 26-29 recite a genus of protein crystal structures of residues 125-391 of SEQ ID NO:1. In this case, the specification discloses only a single crystal structure of residues 125-391 of SEQ ID NO:1, *i.e.*, the 3-D structure of residues 125-391 of SEQ ID NO:1 having the structural coordinates of Figure 3. Other than this single disclosed species, the specification fails to describe any other protein crystal structure of residues 125-391 of SEQ ID NO:1, which

encompasses widely variant species, including any 3-D conformation of residues 125-391 of SEQ ID NO:1, either liganded or unliganded. As noted by Aleshin et al. (*supra*), a single polypeptide can have multiple conformations (see particularly p. 43, right column and Figure 1). As stated above, MPEP § 2163 states "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." As such, the single disclosed species of protein crystal structures of residues 125-391 of SEQ ID NO:1 fails to describe all protein crystal structures as encompassed by the claims.

[12] The scope of enablement rejection of claim(s) 1, 4-6, 9, and 12-15 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action. Claims 17 and 26-30 are included in the instant rejection. Thus, claims 1, 4-6, 9, 12-15, 17, and 26-30 are rejected.

RESPONSE TO ARGUMENT: Applicant argues the claims as amended are all drawn to compositions and methods using residues 125-391 of SEQ ID NO:1, which has been crystallized by applicant, or SEQ ID NO:3, both of which are shown in Figure 1. According to applicant, the rejection is overcome by this amendment.

Applicant's argument is not found persuasive. The examiner maintains the position that the specification fails to enable all crystals and methods as broadly encompassed by the claims. While the examiner acknowledges the amendment to limit

the polypeptide of the crystal or method to residues 125-391 of SEQ ID NO:1, claims 1, 4, 17, and 30 nonetheless broadly encompass all crystals of residues 125-391 of SEQ ID NO:1 (claims 1, 4, and 30) or SEQ ID NO:3 (claim 17), unliganded or complexed with any ligand, having any space group, and any unit cell dimensions. While claims 4-6 limit the resolution, space group symmetry, or the unit cell dimensions of the crystalline form, it is noted that, while a crystal may diffract X-rays to a resolution of a resolution of 1.9 Å, the space group and unit cell dimensions are completely undefined, or while a crystal may have space group $P6_122$, the unit cell dimensions are completely undefined, or while a crystal may have unit cell dimensions of a=80.45 Å, b=80.45 Å, and c=172.18 Å, the space group, which defines the symmetry of the crystal, is completely undefined. Claim 9 broadly encompasses all methods of crystallizing residues 411-686 of SEQ ID NO:1 under any crystallization conditions. Claims 15 and 26-29 broadly encompass all protein crystal structures obtained from said crystal, having any conformation, including homology models, and their use in any method considered to be "rational drug design" for identifying an entity that associates with the protein, and optionally measuring any activity of the protein when contacted with the entity. The specification discloses only a single working example of the claimed crystal, *i.e.,* a crystal of residues 125-391 of SEQ ID NO:1 in complex with ATPγS having the space group symmetry $P6_122$ and having vector lengths a=b=80.45 Å, and c=172.18 Å (p. 24, Table 6), which diffracts X-rays to a resolution of 1.9 Å (specification at pp. 24-25, Table 6), only a single method for its crystallization, *i.e.,* the method disclosed at p. 48, ¶¶ [00198] and [0199] of the specification, only a single working example of the recited protein crystal structure, *i.e.,*

the 3-D structure of residues 125-391 of SEQ ID NO:1 in complex with ATPγS having the structural coordinates of Figure 3, and only a single method of "rational drug design," *i.e.,* using the structure of residues 125-391 of SEQ ID NO:1 in complex with ATPγS having the structural coordinates of Figure 3 to perform a fitting operation between an entity and the computer model and analyzing the results of the fitting operation to quantify the association between the entity and the model, and only one "activity" of the protein that can be measured, *i.e.,* kinase activity. The specification fails to disclose any other working examples or guidance for making other protein crystals of residues 125-391 of SEQ ID NO:1 or SEQ ID NO:3 under any other conditions with an expectation of obtaining diffraction-quality crystals. Further, the specification fails to disclose any other working examples of guidance for making any other protein crystal structure of residues 125-391 of SEQ ID NO:1 with an expectation that the 3-D structure represents a biologically-relevant conformation so that the structure can be used in accordance with the asserted utility of determining the 3-D structure of Aurora kinase and the design of small molecule inhibitors (p. 2, paragraphs [0006] and [0007]). As noted in the prior Office action – and undisputed by application – the state of the art at the time of the invention acknowledges a **high** level of unpredictability for making a protein crystal. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999; cited in the prior Office action) teaches that "[c]rystallization is usually quite difficult to achieve" (p. 375) and that "[w]ell-ordered crystals...are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is

impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Further, regarding the resolution of a structure, Branden et al. teaches that "the structures of only a few small proteins have been determined" at a resolution as low as 1 Angstrom (p. 382, middle), which is encompassed by the claims. Also, Drenth et al. ("Principles of X-ray Crystallography," Springer, New York, 1995; cited in the prior Office action) teaches that "[t]he science of protein crystallization is an underdeveloped area" and "[p]rotein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal nor can one predict the space group symmetry or unit cell dimensions of the resulting crystal. As stated above, even a single polypeptide can have multiple crystal forms, however, what form will result from which particular crystallization conditions – if any – remains highly unpredictable as evidenced by the state of the art at the time of the invention. While applicant may argue that because of the similarity in sequence between residues 125-391 of SEQ ID NO:1 and SEQ ID NO:3, a crystal of SEQ ID NO:3 would have the same space group and unit cell dimensions, there is no way to predict *a priori* the space group and unit cell dimensions of a protein, as evidenced by the references of Kierzek et al. (cited in the prior Office action; see cited relevant teachings) and Buts et al. (*Acta Crystallogr. D.*, vol. 61, pages 1149-1159, 2005), which teaches that even a single amino acid mutation can alter the space group symmetry and unit cell dimensions of a crystallized protein. Further, it is noted that the use of homology models for identifying binding partners is highly unpredictable as evidenced by the reference of Lambert et al.

(US Patent Application Publication 2004/0137518), which teaches that "[p]otential or existent homology models cannot provide the necessary degree of specificity" in the *in silico* design of modulators (p. 3, ¶[0017]). While methods of protein crystallography were known at the time of the invention, it was not routine in the art to make all polypeptide crystals as encompassed by the claims and screen for those that are diffraction-quality under any crystallization conditions as encompassed by the claims, diffract those crystals, and to determine those polypeptide crystal structures that represent biologically-relevant macromolecules.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make and use all crystals and make and use all three-dimensional structures and methods of "rational drug design" as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Claim Rejections - 35 USC § 102

[13] Claim 30 is rejected under 35 U.S.C. 102(b) as being anticipated by Plowman et al. (US Patent 5,962,312).

The claim is drawn to a composition comprising a protein consisting of residues 125-391 of SEQ ID NO:1. The term "composition" in claim 30 can be interpreted as a

polypeptide and thus claim 30 can be interpreted as meaning a polypeptide comprising a protein consisting of residues 125-391 of SEQ ID NO:1.

The reference of Plowman et al. teaches a polypeptide, SEQ ID NO:4, that comprises amino acids 125-391 of SEQ ID NO:1 herein (see Appendix A). This anticipates claim 30 as written.

Examiner Comment/Clarification

[14] It is noted that claims 1 and 9 have been amended to recite "residues 125-391 of SEQ ID NO:1," wherein the original claim recites the range of residues 126-388 of SEQ ID NO:1. MPEP § 2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" (MPEP 8th Ed., October 2006 Revision at pp. 2100-176 and 2100-183). Although applicant fails to "show support" for the amended range of amino acids as required by MPEP § 2163, the amendment does not raise the issue of new matter as the range of amino acids 125-391 of SEQ ID NO:1 is supported in the original application at, *e.g.,* p. 2, paragraph [008].

[15] The term "composition" in claim 17 can be interpreted as a polypeptide and thus claim 17 can be interpreted as meaning a polypeptide comprising a protein consisting of SEQ ID NO:3. Although the claim does not expressly recite "purified" or "isolated" with respect to the recited "composition," the "composition" of claim 17 has not been rejected under 35 U.S.C. 101 as claiming non-statutory subject matter. It is noted that the protein of SEQ ID NO:3 has an N-terminus that does not appear to be naturally-occurring (see

specification at p. 47, paragraph [00196]), and thus the protein sequence itself is inherently indicative of the hand of the inventor.

Conclusion

[16] Status of the claims:

- Claims 1, 4-6, 9, 12-15, and 17-30 are pending.
- Claims 18-25 are withdrawn from further consideration.
- Claims 1, 4-6, 9, 12-15, 17, and 26-30 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656

APPENDIX A

Seq1 is amino acids 125-391 of SEQ ID NO:1

Seq2 is SEQ ID NO:4 of Plowman et al., US Patent 5,962,312

Full-length alignment between two sequences

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>>Seq2                                                    (1105 aa)
 s-w opt: 4673  Z-score: 5728.9  bits: 1071.2 E():    0
Smith-Waterman score: 4673;  100.000% identity (100.000% ungapped) in 730 aa overlap (1-730:341-
1070)

                                        10        20        30
Seq1                                  LYSARGGLNTRPALALEGLASPPHEGLILE
                                      ::::::::::::::::::::::::::::::
Seq2    LEALASERLYSGLNLYSASNGLGLSERLYSLYSARGGLNTRPALALEGLASPPHEGLILE
               320       330       340       350       360       370

                40        50        60        70        80        90
Seq1    GLYARGPRLEGLYLYSGLYLYSPHEGLYASNVALTYRLEALAARGGLLYSGLNSERLYSP
        ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
Seq2    GLYARGPRLEGLYLYSGLYLYSPHEGLYASNVALTYRLEALAARGGLLYSGLNSERLYSP
               380       390       400       410       420       430

               100       110       120       130       140       150
Seq1    HEILELEALALELYSVALLEPHELYSALAGLNLEGLLYSALAGLYVALGLHISGLNLEAR
        ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
Seq2    HEILELEALALELYSVALLEPHELYSALAGLNLEGLLYSALAGLYVALGLHISGLNLEAR
               440       450       460       470       480       490

               160       170       180       190       200       210
Seq1    GARGGLVALGLILEGLNSERHISLEARGHISPRASNILELEARGLETYRGLYTYRPHEHI
        ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
Seq2    GARGGLVALGLILEGLNSERHISLEARGHISPRASNILELEARGLETYRGLYTYRPHEHI
               500       510       520       530       540       550

               220       230       240       250       260       270
Seq1    SASPALATHRARGVALTYRLEILELEGLTYRALAPRLEGLYTHRVALTYRARGGLLEGLN
        ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
Seq2    SASPALATHRARGVALTYRLEILELEGLTYRALAPRLEGLYTHRVALTYRARGGLLEGLN
               560       570       580       590       600       610

               280       290       300       310       320       330
Seq1    LYSLESERLYSPHEASPGLGLNARGTHRALATHRTYRILETHRGLLEALAASNALALESE
        ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
Seq2    LYSLESERLYSPHEASPGLGLNARGTHRALATHRTYRILETHRGLLEALAASNALALESE
               620       630       640       650       660       670

               340       350       360       370       380       390
Seq1    RTYRCYSHISSERLYSARGVALILEHISARGASPILELYSPRGLASNLELELEGLYSERA
        ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
Seq2    RTYRCYSHISSERLYSARGVALILEHISARGASPILELYSPRGLASNLELELEGLYSERA
               680       690       700       710       720       730

               400       410       420       430       440       450
Seq1    LAGLYGLLELYSILEALAASPPHEGLYTRPSERVALHISALAPRSERSERARGARGTHRT
        ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
Seq2    LAGLYGLLELYSILEALAASPPHEGLYTRPSERVALHISALAPRSERSERARGARGTHRT
               740       750       760       770       780       790

               460       470       480       490       500       510
Seq1    HRLECYSGLYTHRLEASPTYRLEPRPRGLMETILEGLGLYARGMETHISASPGLLYSVAL
        ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
Seq2    HRLECYSGLYTHRLEASPTYRLEPRPRGLMETILEGLGLYARGMETHISASPGLLYSVAL
               800       810       820       830       840       850
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              520       530       540       550       560       570
Seq1   ASPLETRPSERLEGLYVALLECYSTYRGLPHELEVALGLYLYSPRPRPHEGLALAASNTH
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
Seq2   ASPLETRPSERLEGLYVALLECYSTYRGLPHELEVALGLYLYSPRPRPHEGLALAASNTH
              860       870       880       890       900       910

              580       590       600       610       620       630
Seq1   RTYRGLNGLTHRTYRLYSARGILESERARGVALGLPHETHRPHEPRASPPHEVALTHRGL
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
Seq2   RTYRGLNGLTHRTYRLYSARGILESERARGVALGLPHETHRPHEPRASPPHEVALTHRGL
              920       930       940       950       960       970

              640       650       660       670       680       690
Seq1   GLYALAARGASPLEILESERARGLELELYSHISASNPRSERGLNARGPRMETLEARGGLV
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
Seq2   GLYALAARGASPLEILESERARGLELELYSHISASNPRSERGLNARGPRMETLEARGGLV
              980       990      1000      1010      1020      1030

              700       710       720       730
Seq1   ALLEGLHISPRTRPILETHRALAASNSERSERLYSPRSER
       ::::::::::::::::::::::::::::::::::::::::
Seq2   ALLEGLHISPRTRPILETHRALAASNSERSERLYSPRSERASNCYSGLNASNLYSGLSER
             1040      1050      1060      1070      1080      1090

Seq2   ALASERLYSGLNSER
             1100
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